CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022406Orig1s000

OTHER ACTION LETTER(s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-406

COMPLETE RESPONSE

Johnson and Johnson Pharmaceutical Research and Development
Attention: Andrea F. Kollath, DVM
Director, Regulatory Affairs
920 Route 202, P.O. Box 300
Raritan, NJ 08869

Dear Ms. Kollath:

Please refer to your new drug application (NDA) dated July 28, 2008, received July 28, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xarelto™ (rivaroxaban) tablets.

We acknowledge receipt of your amendments dated August 11, October 15, November 4, 5, 21, 24, and 25, December 1,16, 18, 19, and 24, 2008; January 6, 13, 23(3), 28(2), 27, 29, and 30, February 2(2), 13, 20, 24, and 25(2), March 2, 3, 4, 6, 11(2), 18(2), 25, and 26, April 1(2), 7, 17, 24, 27, and 30(2), May 1, 5(2), 11, 18, 20(2) and 21, 2009.

We have completed the review of your application, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

CLINICAL

1. Investigator audits of a total of 11 clinical investigator sites, your firm as the applicant, and Bayer Pharmaceuticals as the sponsor of the "RECORD" studies (RECORD 1, 2, 3, and 4), were undertaken to evaluate the conduct of these four studies. These studies supplied most of the clinical data in support of the requested indication.

   Clinical Investigator Inspections

   A total of eight clinical investigator inspections by FDA, two each for the following studies, have been completed as part of the data audit for this NDA: RECORD 1, 2, 3, and 4. For the RECORD 1 study, data from the two clinical investigators audited by FDA are considered reliable in support of this NDA. For the RECORD 2 study, data from one of two clinical investigators audited by FDA are not considered reliable in support of this NDA (Dr.

Qingming Yang). For the RECORD 3 study, one of two investigators audited, Dr. Bingfang Zeng, had a field classification of Official Action Indicated (OAI), indicating that serious deficiencies were noted which raised concerns regarding human subjects protection, although the data appeared acceptable for use in support of the NDA. For the RECORD 4 study, data from one of two audited clinical investigators are not considered reliable in support of this NDA (Dr. Michael Murray).

In addition to these eight clinical investigator inspections that were conducted following the NDA submission, two additional clinical investigators were inspected prior to the NDA submission as a result of complaints. These complaints pertained to the RECORD 2 study (Dr. Corces) and the RECORD 4 study (Dr. Loucks). Based upon the inspection findings, the data from both of these sites are considered unreliable.

The data from the five sites listed above are considered unreliable for the following reasons:

- Failure to conduct the study according to the signed investigator statement and the investigational plan [21 CFR 312.60].
- Failure to report adverse events to the sponsor [21 CFR 312.64].
- Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the inspection [21 CFR 312.62 (b)].
- Failure to obtain adequate informed consent [21 CFR 50]
- Failure to maintain drug accountability records [21 CFR 312.62 (a)]
- Failure to report to the IRB all unanticipated problems involving risk to human subjects [21 CFR 312.66].

Bayer Pharmaceuticals informed us of data integrity issues pertaining to an additional RECORD 4 study clinical investigator, Dr. Ricardo Esquivel in Naulcapan, Mexico. These issues included an inability to confirm that study medication was administered consistent with protocol expectations, due to a systematic discarding of medical records documenting study drug administration.

Sponsor Inspection

Inspection of Bayer Pharmaceuticals as the sponsor of the four RECORD 4 studies revealed that the sponsor failed to 1) ensure proper monitoring of the study, 2) to ensure the study was conducted in accordance with the protocol and/or investigational plan, and 3) to ensure that FDA and all investigators were promptly informed of significant new adverse effects or risks.

In order to address the issues outlined above we request that you:

a. Provide the following information regarding your clinical data quality assurance (QA) audit program that was in place for the four RECORD studies:

i. A report of your QA audit plan, including your plan for securing compliance from non-compliant clinical investigators. Include copies of any Standard Operating Procedures (SOPs) that were in place during conduct of the study to address the means by which corrective actions were to be taken if or when you or the applicable contract research organization (CRO) identified noncompliant clinical investigators.

ii. A report of your audit findings, including any corrective actions taken and final outcomes for the Yang, Murray, Corces, Loucks, and Esquivel sites and for all other sites you audited under your QA program.

iii. A description of any clinical investigators terminated for non-compliance. Provide a list of these clinical investigators, their sites, the specific violations, and whether the data were included in the NDA submission.

b. Describe Bayer's QA program with respect to the oversight of CROs that were hired to monitor the clinical sites, including (b) (4) for the RECORD 4 study. Describe the procedures implemented to make sure that the CROs adequately monitored the clinical sites. In your response, include the following information:

i. How was Bayer kept apprised by the CROs concerning monitoring of the clinical sites during the course of the study? Specifically, what information did the CROs provide? Provide a list of non-compliant clinical study sites reported by the CROs.

ii. How did Bayer review the information obtained from the CROs, during the course of the study and at the end of the study? What monitoring information was kept at the end of the study?

iii. What actions did Bayer take based on the monitoring reports?

c. Provide assurance that the clinical data obtained from the RECORD 1, 2, 3, and 4 studies are reliable. Specifically, perform an additional audit and supply the results of this audit within your response to this letter. Within your response, include:

i. A copy of your audit plan, including the following information:

- How many clinical sites were to be audited, how many subject records were examined, and a description of the process for selection of the audited sites.

- If not all subject records at a given clinical site were to be audited, describe how subject records were sampled and how the specific data from each subject were audited.

ii. The timeline for completion of your audit (plan finalization, start date, completion date, report finalization date).

iii. In addition to any other information within your audit report, address the following questions or requests:

- At each site audited, how many violations involved each of the following specific issues? For each specific violation, list the clinical sites involved and provide a breakdown by treatment group for each site and overall for the four RECORD studies.
    - Enrollment of subjects that did not meet study eligibility criteria.
    - Failure of the Principal Investigator to ensure that all associates and colleagues assisting in the investigation were meeting the commitments of the study protocol.
    - Failure to report adverse events and serious adverse events
    - Failure to randomize subject preoperatively
    - Failure to obtain informed consent from all subjects
- List all clinical sites where either Bayer or CRO monitoring is determined to be ineffective, either in identifying significant violations or in taking actions towards securing compliance (such as notifying the sponsor).

2. The supplied clinical data are insufficient to fully characterize a potential risk for serious liver toxicity. We request the following information:

a. A report that assesses the potential signal for severe liver toxicity in your major on-going clinical studies of patients with atrial fibrillation (the "ROCKET" studies). Provide this report in a manner that does not compromise the analytical integrity of these studies. Base this report upon the findings from a data safety monitoring board's review of the clinical information for patients reported to have serum alanine aminotransferase (ALT) values greater than three times the upper limit of normal along with serum total bilirubin values greater than twice the upper limit of normal. The board's review should, at a minimum, consist of the review of all available clinical data for the index patients along with the treatment assignment. In reviewing these data, the board should consider any possible imbalance in the occurrence of the liver test abnormalities as well as each patient's clinical

features, particularly those related to liver abnormalities. We welcome a discussion with you to address the most appropriate method to report the board's findings to us.

b. A report of the safety findings from the rivaroxaban post-marketing experience outside the United States. Include tabular and text summaries of spontaneously reported adverse events and an estimate of the numbers of patients exposed in the market place.

c. A report that provides a summary of post-marketing studies initiated outside the United States, to include a description of the study designs, a status update (e.g., date of initiation, numbers of enrolled subjects) as well as a summary of adverse events detected in these studies. Additionally, provide a copy of the protocol for the "observational" post-marketing study you cited at the March 19, 2009, Advisory Committee.

d. Provide a final report for the "ATLAS ACS TIMI 46" study, including electronic datasets sufficient to verify the safety and efficacy data.

PRODUCT QUALITY

3. DMF 21580 is inadequate in support of this NDA.

4. DMF 21581 is inadequate in support of this NDA.

5. DMF 21592 is inadequate in support of this NDA.

6. The drug substance information is not adequate in that it does not meet 21 CFR 314.50(d)(1)(ii). Insufficient information is provided to confirm nomenclature, description, physicochemical properties, specifications, the primary stability protocol, the post-approval stability commitment and primary stability data.

7. The drug product specification, as provided by Bayer HealthCare Pharmaceuticals, Inc. is inadequate because it does not propose analytical methods for test parameters Additionally, the proposed acceptance criteria for uniformity of dosage units do not meet the current USP requirements.

8. The proposed acceptance criteria for uniformity of dosage units and dissolution are different between Bayer HealthCare Pharmaceuticals and Janssen Ortho Pharmaceuticals. Justify this difference or alternatively, resolve the discrepancy.

9. The currently-proposed acceptance criterion for dissolution is not acceptable and is recommended to be Q=(b) (4) at 15 minutes.

10. The container and closure system is not adequately described.

11. The proposed stability study is inadequate in that no stability data are submitted for pilot or commercial batches. In addition, a postapproval stability protocol and stability commitment were not submitted for Bayer Pharmaceuticals, Inc.

CLINICAL PHARMACOLOGY

We have the following additional comment for you to address in your response to this letter. This clinical pharmacology request is not a basis for our inability to approve your application. However, we request a response to facilitate our review of the proposed labeling and the need for any post-marketing expectations.

12. Provide a description of your plans to develop a lower strength formulation to be used for dose modification in certain special populations of patients.

LABELING

Package Insert

13. We reserve comment on the Package Insert until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html.

Container Label and Carton Labeling

14. Please submit draft labeling revised as follows.

    a. Revise the established name on the bulk container label (30 tablets) to include the dosage form as follows: 'rivaroxaban tablets'.

    b. The size of the graphic on the principal display panel is more prominent than the size of the established name and proprietary name. The proprietary name, established name and strength should be the most prominent information on the container label and carton labeling.

    c. Delete or relocate to the side panel the [redacted] (b) (4) statement as itcrowds the principal display panel on the container label and carton labeling.

    d. Provide a more specific description (e.g., color, shape, size, resin) for bottles used as containers (NDC 50458-580-30) in the How Supplied section. In addition, include the carton as a container for [redacted] (b) (4) blister packs, and provide a description in the How Supplied Section (section 16) of the package insert labeling.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

    - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
    - Present tabulations of the new safety data combined with the original NDA data.
    - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
    - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take one of the other actions available under 21 CFR 314.110. If you do not take one of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry *Formal Meetings With Sponsors and Applicants for PDUFA Products*, February, 2000 (http://www.fda.gov/cder/guidance/2125fnl.htm).

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have questions, contact Marcus Cato, Regulatory Project Manager, at (301) 796-3903.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, MD
Director
Office of Oncology Drug Products
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Richard Pazdur

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